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## Presentation of adult mitochondrial epilepsy

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## ARTICLE INFO

## Article history:

Received 1 August 2012

Received in revised form 6 November 2012

Accepted 7 November 2012

## Keywords:

Mitochondrial disorder

Epilepsy

Seizure

EEG

Central nervous system involvement

Antiepileptic drugs

## ABSTRACT

**Purpose:** Mitochondrial disorders (MIDs) frequently manifest phenotypically as epilepsy (mitochondrial epilepsy). Mitochondrial epilepsy occurs in early-onset as well as late-onset syndromic and non-syndromic MIDs. We were interested in the types of epilepsy, the prevalence of mitochondrial epilepsy, the type and effectiveness of treatment, and in the outcome of adult MID patients with epilepsy.

**Methods:** We retrospectively evaluated adult patients with syndromic or non-syndromic MIDs and epilepsy. MIDs were classified according to the modified Walker criteria as definite, probable, and possible.

**Results:** Epilepsy in adult patients with a MID was classified as "structural/metabolic" in two-thirds of the cases and as "genetic" in one-third of the cases. Although all types of seizures may occur in mitochondrial epilepsy, adult patients most frequently presented with generalised tonic-clonic seizures, partial seizures, convulsive status epilepticus, or non-convulsive status epilepticus. Cerebral imaging was normal in one-third of the patients. Two-thirds of the adult patients with mitochondrial epilepsy who took antiepileptic drugs received monotherapy, one-third combination treatment. The antiepileptic drugs most frequently administered included levetiracetam, lamotrigine, valproic acid, and gabapentin. Antiepileptic drugs were usually well tolerated and the outcome favourable.

**Conclusions:** Adult mitochondrial epilepsy appears to be less frequent than previously believed but the prevalence strongly depends on patient selection. Mitochondrial epilepsy is most frequently "structural/metabolic". AEDs recommended for mitochondrial epilepsy include levetiracetam, lamotrigine, gabapentin and lacosamide. The outcome of mitochondrial epilepsy may be more favourable if mitochondrion-toxic AEDs are avoided. Only if non-mitochondrion-toxic AEDs are ineffective, mitochondrion-toxic AEDs may be used.

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**Abbreviations:** AED, antiepileptic drug; AHS, Alpers–Huttenlocher-syndrome; CNS, central nervous system; COX, Cytochrome-c-oxidase; CPEO, mitochondrial or nuclear chronic progressive external ophthalmoplegia; CSF, cerebro-spinal fluid; EMP, encephalomyopathy; EP, encephalopathy; EPC, epilepsia partialis continua; IOSCA, infantile-onset spino-cerebellar ataxia-syndrome; KSS, Kearns-Sayre-syndrome; LBSL, leucencephalopathy with brain stem and spinal cord involvement and lactacidosis; LE, leucencephalopathy; LHON, Leber's hereditary optic neuropathy; MDDS, mitochondrial DNA depletion syndrome; MELAS, mitochondrial encephalopathy, lactacidosis and stroke-like episodes-syndrome; MEMSA, myoclonic epilepsy, myopathy and sensory ataxia-syndrome also known as SCAE; MERRF, myoclonic epilepsy with ragged-red fibres-syndrome; LS, Leigh-syndrome; MID, mitochondrial disorder; MIDD, maternally-inherited diabetes and deafness; MILS, maternally-inherited Leigh-syndrome; MIRAS, mitochondrial recessive ataxia syndrome; NARP, neuropathy, ataxia and retinitis pigmentosa; SCAE, spino-cerebellar ataxia with epilepsy; SDH, succinate-dehydrogenase; SUDEP, sudden unexplained death in epilepsy; TCS, tonic-clonic seizure.

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## 1. Introduction

Epilepsy is a frequent phenotypic manifestation of syndromic as well as non-syndromic mitochondrial disorders (MIDs).<sup>1</sup> According to the new classification of epilepsies, epilepsy in MIDs may have a genetic or structural/metabolic cause in case of a previous cerebral lesion or dysfunction, or may be of unknown aetiology in case of an undetermined cause.<sup>2</sup> Structural/metabolic epilepsy in MIDs may be due to atherothrombotic or embolic ischaemic stroke, a stroke-like lesion, atrophy, white matter lesions, grey matter lesions, cerebrospinal fluid (CSF)-lactacidosis, cardiac involvement in the MID, endocrinopathy, or due to other disorders, which may cause structural central nervous system (CNS) disease.<sup>3</sup> Epilepsy may be a collateral manifestation of a MID or the dominant feature of the phenotype, such as in mitochondrial encephalopathy, lactacidosis and stroke-like episodes (MELAS)-syndrome, myoclonic epilepsy with ragged-red fibres (MERRF)-syndrome, Leigh-syndrome, myoclonic epilepsy, myopathy and sensory ataxia (MEMSA)-syndrome, also known as spino-cerebellar ataxia with epilepsy (SCAE),

mitochondrial recessive ataxia syndrome (MIRAS), sensory ataxia with neuropathy, dysarthria and ophthalmoparesis (SANDO)-syndrome, or Alpers–Huttenlocher-syndrome (AHS).<sup>3</sup> Little is known about the predominant types and frequency of seizures, treatment and outcome of epilepsy in adult patients with a MID. The present study was therefore designed to describe: (1) which types of epilepsy occur in adult MIDs, (2) what the prevalence of definite, probable or possible mitochondrial epilepsy is in adults, (3) what the most effective treatment is, and (4) what outcome can be most likely expected in these patient groups.

## 2. Patients and methods

Retrospectively evaluated were patients with syndromic or non-syndromic MIDs and epilepsy, who attended in- or outpatient units of the Krankenhaus Rudolfstiftung. MIDs were classified according to the modified Walker criteria as definite, probable, and possible.<sup>4</sup> A MID was classified as “definite” if the clinical presentation was indicative of a MID and if there was biochemical (deficiency of complex I, II, or IV of the respiratory chain) or genetic evidence of a mitochondrial defect. A MID was classified as “probable” if the clinical presentation was indicative of a MID and if immuno-histological investigations on muscle biopsy showed COX-negative fibres, ragged-red-fibres, SDH-hyper-reactive fibres, or abnormally shaped or structured mitochondria with or without paracrystalline inclusions or glycogen or fat depositions on electron microscopy.<sup>4</sup> A MID was classified as “possible” if the clinical presentation suggested a MID (Table 1) and if instrumental investigations other than a muscle biopsy were indicative of a MID (Table 2).<sup>4</sup> The clinical presentation was considered “suggestive” of a MID if at least 3 of the clinical findings listed in Table 1 were present and if additionally at least 3 instrumental investigations listed in Table 2 were present or if <3 clinical abnormalities and >10 abnormalities on instrumental investigations were found in a single patient.

Included were all patients in whom seizures had occurred previously without requiring antiepileptic drug (AED) treatment at the time of the consultation and those who were taking AED treatment at the time of attendance or had experienced seizures during the last year prior to the consultation. Epilepsy was classified according to its aetiology following the classification of

**Table 2**

Unexplained instrumental findings other than a muscle biopsy or genetic testing indicative of a MID.<sup>1</sup>

Cerebral imaging
Basal ganglia calcification, focal cerebral atrophy, white matter lesions, stroke-like lesion, optic atrophy, pituitary adenoma, empty sella
PNS
Polyneuropathy, motor neuron disease, myopathy
Eyes
Pigmentary retinopathy, cataract, glaucoma, prolonged visually evoked potentials
Ears
Hypoacusis on audiometry
Serum/CSF tests
Elevated serum/CSF lactate, elevated CSF protein, pleocytosis, recurrent CK-elevation, elevated liver function parameters, elevated amylase, renal insufficiency, hyperlipidemia, hyperuricemia
Blood cells
Anaemia, thrombopenia, thrombocytosis, leucopenia, eosinophilia
Heart
Hypertrophic cardiomyopathy, dilative cardiomyopathy, left ventricular hypertrabeculation (noncompaction), Takotsubo syndrome, arrhythmias
Kidneys
Kidney cysts, nephrolithiasis, renal failure
Guts
Parotitis, hepatopathy, liver cysts, pancreatitis, pancreatic cysts, diverticulosis, “nonspecific” colitis
Endocrinium
Osteoporosis, hypopituitarism, hypocorticism, diabetes, hypoadosteronism, hypothyroidism, hyperthyroidism, hypogonadism
Vessels
Atherosclerosis, arterial stenosis, occlusion, aneurysm, ectasia, dissection, or rupture
Skin
Madarosis, psoriasis, lipomatosis

the International League against Epilepsy (ILAE) 2010<sup>2</sup> as genetic or presumed genetic, as structural or metabolic, or unknown. Seizure types were classified as generalised or focal.<sup>2</sup> Epilepsy in MIDs with stroke-like episodes was classified as genetic but not as structural/metabolic since the stroke-like lesion was not regarded as prerequisite for the development of seizures.

## 3. Results

Altogether, 444 patients were classified as MID during the observation period of 4 years, 15 as definite, 54 as probable and 375 as possible MID (Table 3). Insufficient or inconclusive data concerning epilepsy were available in 3 patients (Table 3). Among the remaining 441 patients, epilepsy was associated with a MID in 60 patients: in 3 cases MID was categorised as definite, in 12 as probable, and in 45 as possible (Table 3). Among the 3 patients with definite MID and epilepsy one presented with syndromic MID (MELAS-syndrome (respiratory chain complex defect, >2% ragged-red fibres, >2% COX-negative fibres)) and two with non-syndromic MIDs. One of the patients with definite non-syndromic MID had a multisystem disease with multiple respiratory chain complex deficiencies and the second patient epilepsy and cardiomyopathy with complex-I defect, >2% ragged-red fibres, >2% COX-negative fibres, and para-crystalline inclusions on electron microscopy. The number of abnormalities listed in Tables 1 and 2 found in the 45 possible MIDs are presented in Table 4.

Among the 60 patients with epilepsy 38 were female and 22 male. Mean age was 67.2 years (range: 35–90 years). None of the patients with probable MIDs and epilepsy fitted into a distinct mitochondrial syndrome. Epilepsy had a structural/metabolic aetiology in 39 cases. It was attributed to previous ischaemic stroke in 14 patients, to chronic alcohol consumption in 8, to cerebral atrophy in 7, to a cerebral tumour in 3, to a head trauma, encephalitis, or hypoxia each in 2, and to superficial siderosis in 1 (Fig. 2). In 21 patients, epilepsy was classified as genetic,

**Table 1**  
History, symptoms and signs suggestive of a MID.<sup>1</sup>

PNS
Double vision, ptosis, ophthalmoparesis, dropped head, camptocormia, cervical spine syndrome, limb weakness, muscular respiratory insufficiency, exercise intolerance, fatigue, easy fatigability, sore muscles, myalgia, muscle cramps, sensory disturbances, sensory ataxia, muscle rupture
CNS
Disorientation, confusion, autism, psychosis, lethargy, cognitive decline, dementia, seizures, stroke-like episode, ischaemic stroke, hypersomnia, migraine, migraine-like headache, cluster headache, cerebellar ataxia, movement disorder, transverse syndrome
Eyes
Visual impairment, blurred vision, visual field defects, painful bulbs
Ear
Hypoacusis, acute hearing loss, tinnitus
Endocrine organs
Short stature, sicca-syndrome, hyperhidrosis, impotence, hypogonadism, adynamia
Heart
Palpitations, orthopnoea, exertional dyspnoea, leg oedema, neck vein distension, recurrent syncope, sudden cardiac death
Gastrointestinal
Dysphagia, vomiting, diarrhoea, obstipation, jaundice, colics, pancreatitis
Kidneys
Colics from nephrolithiasis
Skeleton
Scoliosis, arthralgia, dysmorphism

**Table 3**  
Results of the present investigation.

	Total	Definite	Probable	Possible
NP screened	444	15	54	375
NP insufficient data	3	1	0	2
NP with epilepsy	60 (14%)	3 (20%)	12 (22%)	45 (12%)
NP with genetic epilepsy	21	3	6	12
NP with structural epilepsy	39	0	6	33
Stroke	14	0	2	12
Alcoholism	8	0	2	6
Cerebral atrophy	7	0	0	7
Tumour	3	0	0	3
Encephalitis	2	0	1	1
Hypoxia	2	0	0	2
Trauma	2	0	0	2
Superficial siderosis	1	0	0	1
NP with focal seizures	6	0	0	6
NP with generalised seizures	51	2	12	37
NP with focal + generalised seizures	2	1	0	1
Seizure type unknown	1	0	0	1
NP receiving treatment	48	3	9	36
LEV	12	0	2	10
LEV, OXC	2	0	0	2
LEV, LTG, LAC	2	1	0	1
LEV, LTG, OXC	1	0	0	1
LTG	13	0	4	9
LTG, LAC	1	1	0	0
LTG, GBP	1	0	0	1
VPA	1	0	1	0
VPA, LEV	3	0	0	3
VPA, LTG	1	0	0	1
VPA, GBP	1	0	0	1
VPA, TPM	1	0	0	1
VPA, LEV, LTG	1	0	0	1
CBZ	2	0	0	2
CBZ, PRM	1	0	0	1
GBP	4	1	2	1
OXC	1	0	0	1
NP without AED treatment	11	0	3	8
Unknown if on an AED	1	0	0	1

NP, number of patients.

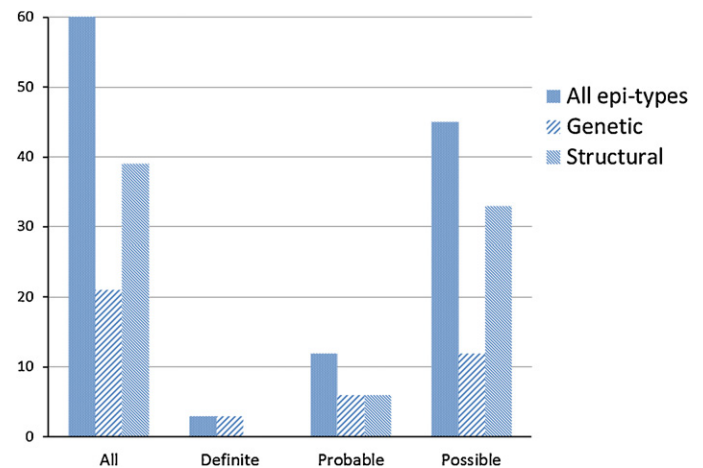
attributable to the proven or presumed genetic defect responsible for the MID, presumably manifesting also in the brain. Among all patients with epilepsy and MID, seizures were generalised in 51 patients, focal in 6 patients, and generalised and focal in 2 patients (Table 3 and Fig. 1). The history was positive for a non-convulsive status epilepticus in three patients and for a convulsive status epilepticus in two patients. Sudden unexplained death in epilepsy (SUDEP) had not occurred in any of the patients.

At the time of the last consultation, 48 patients took AEDs and 11 did not. Reasons for not taking AEDs were general aversion against AEDs, unauthorised discontinuation of AEDs, or previous epilepsy, which no longer required AED treatment. Among those taking AEDs, 33 were on monotherapy, and 15 on polytherapy with

**Table 4**  
Number of abnormalities on the history, symptoms and signs, and on instrumental investigations listed in Tables 1 and 2 among the 45 possible MID patients included.

Number of abnormalities	NP
Three AT1 and 3 AT2	5
Three AT1 and 4 AT2	6
Three AT1 and 5 AT2	7
Three AT1 and 6 AT2	6
Three AT1 and >6 AT2	5
Four AT1 and 3 AT2	3
Four AT1 and 4 AT2	5
Four AT1 and 5 AT2	2
Four AT1 and >5 AT2	4
Five AT1 and 3 or more AT2	1
<3 AT1 but >10 AT2	1

NP, number of patients; AT1, abnormalities of Table 1; AT2, abnormalities of Table 2.

**Fig. 1.** Number of patients with definite, probable, and possible MID who presented with genetic or structural/metabolic epilepsy.

two ( $n = 11$ ) or three AEDs ( $n = 4$ ). The AEDs most frequently used in this study were levetiracetam ( $n = 21$ ), lamotrigine ( $n = 20$ ), and valproic acid ( $n = 8$ ). The AEDs most frequently applied in monotherapy were lamotrigine, ( $n = 13$ ), levetiracetam ( $n = 12$ ), and gabapentin ( $n = 4$ ) (Table 3). The combination therapies most frequently applied were valproic acid with levetiracetam ( $n = 3$ ), levetiracetam with oxcarbazepine ( $n = 2$ ), and levetiracetam with lamotrigine and lacosamide ( $n = 2$ ). Among those receiving levetiracetam 12 were on a monotherapy and nine on a polytherapy with one or two other AEDs. The second most frequently administered AED was lamotrigine. Thirteen patients were on a monotherapy with lamotrigine and 7 took lamotrigine in combination with another AED.

Twenty-five patients with mitochondrial epilepsy attended at least one follow-up visit. In none of these patients epilepsy was refractory. Outcome of the included patients was not systematically investigated in the present study, but among the 25 who repeatedly attended the hospital, seizures were well controlled in the majority of the cases, and only in single patients in whom seizures recurred, the AED dosage had to be adopted or the AED had to be replaced.

#### 4. Discussion

The present study shows that epilepsy occurs in 14% of adult patients with a definite, probable, or possible MID. The prevalence of mitochondrial epilepsy was higher in definite and probable MIDs than in possible MIDs. In 65% of the cases, epilepsy had a structural and in 35% a genetic cause. Seizures were generalised in 85% of the cases, focal in 10%, and focal and generalised in 3%. Eighty percent received an AED therapy but 18% were without AED at the last visit or admission.

Only few studies have been carried out, which have systematically investigated epilepsy phenotypes in the context of MIDs.<sup>5–7</sup> In a study of 23 children with MID and epilepsy, 70% had refractory epilepsy in association with progressive encephalopathy.<sup>5</sup> Patients with epilepsy were more likely to have complex-I defects than children without epilepsy. Patients without epilepsy were more likely to have a complex-III or complex-IV defect than patients with epilepsy.<sup>5</sup> In a study on 48 MID patients with epilepsy, 2 had Ohtahara syndrome, 10 West-syndrome, 12 Lennox–Gastaut syndrome, 2 Landau–Kleffner syndrome, 14 generalised epilepsy, and 8 focal seizures.<sup>6</sup> In a study on 56 children with MID and epilepsy, 2 had a refractory neonatal status epilepticus, 21 myoclonic epilepsy, 8 infantile spasms, 21 refractory/recurrent

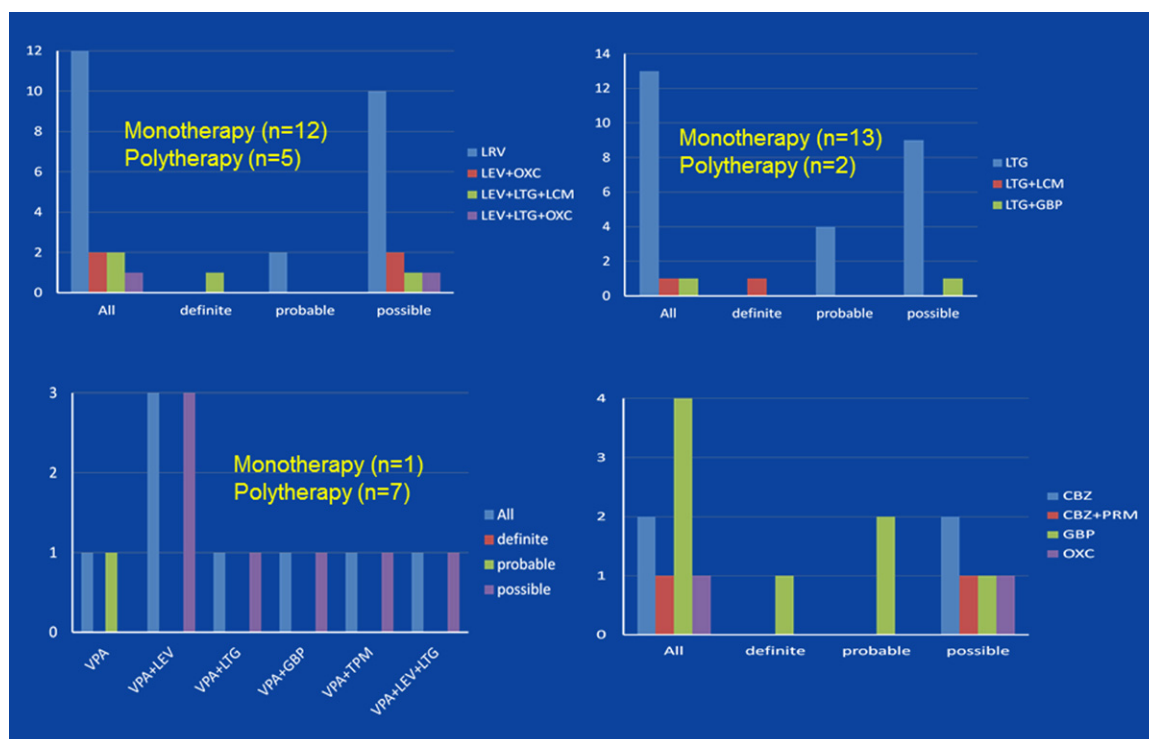


Fig. 2. Causes of structural/metabolic epilepsy among patients with a definite, probable, or possible MID.

status epilepticus, and 4 epilepsy partialis continua.<sup>7</sup> In >80% of these cases, epilepsy was preceded by other phenotypic features of the MID.<sup>7</sup> In the latter study 60% of the patients had more than one seizure type.<sup>7</sup> One study investigating 22 children with definite, probable, or possible MID showed that 17 participants had generalised seizures and 5 partial seizures.<sup>8</sup> Among the 17 patients with generalised seizures, 4 started with focal seizures.<sup>8</sup> It is not clear why none of the cases included in the present study was diagnosed with a specific electroclinical syndrome, myoclonic seizures or epilepsy partialis continua, but these findings may be explained by the fact that only adult patients were included in this study and that the majority of patients described here had probable and possible but not definite MIDs.

Concerning the frequency of epilepsy in patients with MIDs, only limited data are available.<sup>5,9</sup> Seizures have been reported to occur in 25–71% of paediatric patients with biochemically confirmed MID<sup>5,9,10</sup> but in small series of MIDs 100% of the patients with AHS or MERRF-syndrome had developed epilepsy.<sup>10,11</sup> Seizures were reported in about 40% of the patients with Leigh-syndrome<sup>11</sup> and are also a frequent feature of SCO2 mutations but are rare in SURF1 deficiency.<sup>12</sup> In a study of 113 paediatric MID patients 44 (39%) had non-specific encephalopathy and of these 50% had epilepsy.<sup>13</sup> Contrary to these figures in paediatric patients, the prevalence of epilepsy in adult MIDs was only 14% in the present study. The discrepancy could be explained by the poor genotype/phenotype correlation in MIDs, the fact that the present study also included non-biochemically confirmed probable and possible MIDs, and the fact that the prevalence of epilepsy depends on the type of MIDs included in a study. Epilepsy is definitively more frequent in some MIDs than in others. In some of the MIDs epilepsy even dominates the phenotype, such as in MELAS-syndrome, MERRF-syndrome, Leigh-syndrome, MEMSA-syndrome, MIRAS-syndrome, SANDO, pontocerebellar hypoplasia, or AHS.<sup>14</sup> AHS should be particularly suspected in cases with fulminant onset focal epilepsy, epilepsy partialis continua, or

status epilepticus and predominant occipital epileptiform discharges.<sup>15</sup> In the other syndromic MIDs, epilepsy occurs only occasionally. The prevalence of epilepsy may be higher in studies, which include MIDs that are frequently associated with epilepsy as compared to MIDs with low prevalence of epilepsy. A further reason could be the high phenotypic heterogeneity within a syndrome, within a family or sibship, and between families. The prevalence is also dependent on how thoroughly patients with syncope, collapses, falls, states of impaired consciousness, or temporary behavioural, sensory or motor deficits suggestive of a seizure or epileptic state, are further investigated.

Though some of the AEDs given in the present study are mitochondrion-toxic (in particular valproic acid, carbamazepine, and oxcarbazepine),<sup>14</sup> these AEDs were continued if seizure control was acceptable, which was the case in most of these patients, if severe and compromising side effects were absent or tolerable, and if patients did not consent with a change of the AED. However, patients were generally informed about the mitochondrion-toxicity of various AEDs (valproic acid, carbamazepine, phenytoin, phenobarbital, oxcarbazepine) and alternatives to these agents, which include lamotrigine, levetiracetam, gabapentin, and lacosamide were proposed.<sup>14</sup> Levetiracetam and lamotrigine may even exhibit a protective effect against mitochondrial dysfunction.<sup>16</sup> Beneficial effects in addition to the antiepileptic effect have been also reported for valproic acid, carbamazepine, and lamotrigine (antidepressive effect) for pregabalin (anxiolytic effect), and for gabapentin and pregabalin (antineuralgic effect), which have been observed also in patients with MIDs [personal communication]. None of the patients described in this study used the ketogenic diet (high fat, adequate protein, low carbohydrates) although this diet has been found to be particularly effective in MIDs with myoclonic seizures, such as in Dravet syndrome<sup>17</sup> and in patients carrying mtDNA deletions.<sup>11</sup> Vagal nerve stimulation does not seem to be particularly effective in mitochondrial epilepsy.<sup>5,18</sup> Antioxidants have been proposed as adjunctive agents



in mitochondrial epilepsy to reduce oxidative stress produced by excess of free radicals.<sup>19</sup>

In conclusion, this study shows that mitochondrial epilepsy in adults appears less frequently than previously believed but the prevalence is strongly dependent on the selection of MID patients. Mitochondrial epilepsy is most frequently associated with a structural/metabolic cerebral lesion. In one-third of the cases, cerebral imaging is normal. Generalised seizures are considerably more frequent than focal seizures. AEDs recommended for the treatment of mitochondrial epilepsy are levetiracetam, lamotrigine, gabapentin, and lacosamide. Outcome of MID patients with epilepsy is favourable if mitochondrion-toxic AEDs are avoided. Only if epilepsy is refractory to non-mitochondrion-toxic drugs, mitochondrion-toxic AEDs may be tried.

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